inflammatory disease of the bowel, which method comprises intravenous administration. . .

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     (FILE 'USPAT' ENTERED AT 10:58:40 ON 07 DEC 95)
L1           531 S CROHN?
L2         21112 S ANTIBOD? OR IMMUNOGLOBUL? OR IG!
L3           220 S L2 AND L1
L4          1434 S TNF OR (NECROSIS(W)FACTOR#)
L5            35 S L4 AND L2 AND L1
L6            35 S L4(10A)L5
L7             0 S L4(10A)L1
L8             3 S L2(10A)L1


 SESSION WILL BE HELD FOR 30 MINUTES
U.S. Patent & Trademark Office SESSION SUSPENDED AT 11:18:31 ON 07 DEC 95
 07dec95 11:30:56 User214394 Session B17.2
             $1.50    0.050 Hrs File411
     $1.50  Estimated cost File411
     $0.60  SPRNTNET
     $2.10  Estimated cost this search
     $2.14  Estimated total session cost   0.053 Hrs.

SYSTEM:OS  - DIALOG OneSearch
  File 654:US PAT.FULL.  1990-1995/Dec 05
         (c) format only 1995 Knight-Ridder Info
  File 636:IAC Newsletter DB(TM)  1987-1995/Dec 07
         (c) 1995 Information Access Co.
  File 148:Trade & Industry Database(TM)  1976-1995/Dec 07
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  File  16:IAC PROMT(R)  1972-1995/Dec 07
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  File 440:Current Contents Search(R)  1990-1995/Nov W2
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*File 440: Use Format 19 for contents records (LIMIT /CONT)
Use Formats 2 - 9 for individual article records (LIMIT /NCONT)
  File 149:IAC Health & Wellness DB(SM)  76-95/NOV W4
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         (c) 1995 Inst for Sci Info
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         (c) format only 1995 Knight-Ridder Info
  File 445:IMSworld R&D Focus  1991-1995/Dec 01
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Serial No.: 08/192,102
Art Unit: 1806

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7/7/1 (Item 1 from file: 654)
DIALOG(R)File 654:US PAT.FULL.
(c) format only 1995 Knight-Ridder Info. All rts. reserv.

02475179
Utility
CELL SIGNALING INHIBITORS

PATENT NO.: 5,470,878
ISSUED: November 28, 1995 (19951128)
INVENTOR(s): Michnick, John, Seattle, WA (Washington), US (United States of America)
Underiner, Gail E., Brier, WA (Washington), US (United States of America)
Klein, J. Peter, Vashon Island, WA (Washington), US (United States of America)
Rice, Glenn C., Seattle, WA (Washington), US (United States of America)
ASSIGNEE(s): Cell Therapeutics, Inc, (A U.S. Company or Corporation), Seattle, WA (Washington), US (United States of America)
[Assignee Code(s): 32953]
APPL. NO.: 8-164,081
FILED: December 08, 1993 (19931208)

CROSS-REFERENCE TO RELATED APPLICATION

This application is a Continuation-in-Part Application of U.S. application Ser. No. 08-040,820 filed Mar. 31, 1993, now abandoned.

FULL TEXT: 2585 lines

ABSTRACT

Therapeutic compounds have the formula:(X)j-(non-cyclic core moiety),

j being an integer from one to three, the core moiety is non-cyclic and X is a racemic mixture, R or S enantiomer, solvate, hydrate, or salt of: [See structure in original document] *C is a chiral carbon atom, n is an integer from one to four (preferably from one to three), one or more carbon atoms of (CH sub 2) sub n may be substituted by a keto or hydroxy group, and m is an integer from one to fourteen. Independently, R sub 1 and R sub 2 may be a hydrogen, a straight or branched chain alkane or alkene of up to twelve carbon atoms in length, or --(CH sub 2) sub w R sub 5, w being an integer from two to fourteen and R sub 5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R sub 5 being hydroxy, chloro, fluoro, bromo, or C sub 1-6 alkoxy. Or jointly, R sub 1 and R sub 2 form a

substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. R sub 3 is a hydrogen or C sub 1-3. Or, therapeutic compounds may also have the formula: [See structure in original document] R sub 4 is a hydrogen, a straight or branched chain alkane or alkene of up to eight carbon atoms in length, --(CH sub 2) sub w R sub 5, w being an integer from two to fourteen and R sub 5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R sub 5 being hydroxy, chloro, fluoro, b omo, or C sub 1-6 alkoxy, or a substituted or unsubstituted, saturated or unsaturated heterocyclic group having frone or more carbon atoms of (CH sub 2) sub n is substituted with an oxygen atom or hydroxyl group.

10. A method for treating an autoimmune disease, comprising administering an effective amount of a ompound of claim 1, wherein the auto immune disease is rheumatoid arthritis.

7/7/2 (Item 2 from file: 654)
DIALOG(PCT-EP91-00637 (WO 91EP637)
Section 371 Date: October 02, 1992 (19921002)
Section 102(e) Date: October 02, 1992 (19921002)
Filing Date: April 02, 1991 (19910402)
Publication Number: WO91-15451 (WO 9115451)
Publication Date: October 17, 1991 (19911017)
FULL TEXT: 976 lines

ABSTRACT

A compound of formula (I) or a pharmaceutically acceptable salt thereof: [See structure in original document] wherein: R sub 1 is --CH sub 3 or --CH sub 2 CH sub 3 unsubstituted or substituted by 1 to 3 fluorines;
X is O or S(O) sub s where s=0 to 2;
R sub 2 is C sub 4 -C sub 6 cyclic alkyl, optionally substituted by one to three methyl groups or one ethyl group; --CH sub 2 -cyclopentyl, --CH sub 2 -cyclopropyl, 3-tetrahydrofuranyl, C sub 1-7 alkyl, CH sub 3 or CH sub 2 CH sub 3 substituted by one to three fluorines;
--(CH sub 2) sub n COO(CH sub 2) sub g CH sub 3, or (CH sub 2) sub n O(CH sub 2) sub g CH sub 3, wherein n is 2 to 4 and g is 0 to 2;
R sub 3 represents a moiety of formula (a); [See structure in original document] wherein R sub 4 and R sub 5 each represent hydrogen or R sub 4 and R sub 5 together represent a bond;
B represents >C double bond O, >C double bond S or >CH--R sub 6 wherein R sub 6 represents H, OH, C sub 1-6 alkoxy or C sub 1-6 thioalkoxy; and m and r each independently represents zero or an integer in the range of 1 to 4 wherein m+r represents an integer in the range of from 2 to 4; with the proviso that when R sub 1 is methyl, X is oxygen, R sub 2 is methyl or cyclopenyl, R sub 3 does not represent cyclopent-1,2-ene-3-one.

We claim:

Serial No.: 08/192,102
Art Unit: 1806

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof: [See structure in original document] R sub 1 is --CH sub 3 or --CH sub 2 CH sub 3 unsubstituted or substituted by 1 to 3 fluorine; X is O or S(O) sub s where s=0 to 2;
R sub 2 is C sub 4 - cyclic alkyl, optionally substituted by one to three methyl groups or one ethyl group; --CH sub 2 -cyclopentyl, --CH sub 2 -cyclopropyl, 3-tetrahydrofuranyl, C sub 1-7 alkyl, CH sub 3 or CH sub 2 CH sub 3 substituted by one to three fluorines;
--(CH sub 2) sub n COO(CH sub 2) sub g CH sub 3, or (CH sub 2) sub n O(CH sub 2) sub g CH sub 3, wherein n is 2 to 4 and g is 0 to 2;
R sub 3 represents a moiety of formula (a): [See structure in original document] wherein R sub 4 and R sub 5 each represent hydrogen or R sub 4 and R sub 5 together represent a bond; B represents >C double bond O, >C double bond S or >CH--R sub 6 wherein R sub 6 represents H, OH, C sub 1-6 alkoxy or C sub 1-6 thioalkoxy; and m and r each independently represents zero or an integer in the range of 1 to 4 wherein m+r represents an integer in the range of from 2 to 4; with the proviso that when R sub 1 is methyl, X is oxygen, R sub 2 is [methyl or]cyclopentyl, R sub 3 does not represent cyclopent-1,2-ene-3-one.

2. A compound according to claim 1 in which R sub 1 represents methyl and X represents oxygen.

3. A compound according to claim 1 in which R sub 2 represents unsubstituted C sub 4-6 cycloalkyl.

4. A compound according to claim 1 in which R sub 2 represents cyclopentyl or methyl.

5. A compound according to claim 1 in which R sub 3 is selected from the following structures; [See structure in original document] in which B is C double bond O, CH sub 2, CH sub 2 OH or CH sub 2 OCH sub 3.

6. A compound according to claim 5 in which R sub 3 is of formula b) or c) and B is carbonyl, CH sub 2 OH or CH sub 2 OCH sub 3.

7. A compound selected from the group consisting of:
1-(3-(cyclopentyloxy-4-dimethoxy)-phenyl)-cyclohex-1,2-ene-3-one,
1-methoxy-2-cyclopentyloxy-4-cyclohexylbenzene, and
1,2-methoxy-4-cyclohexyl-benzene.

8. A compound selected from the group consisting of:
3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-2-en-1-one,
3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentan-1-one,
cis-3- (3-cyclopentyloxy-4-methoxyphenyl) cyclopentan-1-ol,
3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-2-en-1-ol,
3-(3-cyclopentyloxy-4-methoxyphenyl)-1-methoxycyclopent-2-ene,
trans-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentan-1-ol, and
cis-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-methoxycyclopentane.

7/7/5 (Item 5 from file: 654)

Serial No.: 08/192,102
Art Unit: 1806

DIALOG(R)File 654:US PAT.FULL.
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02304183
Utility
INHIBITION OF INTERLEUKIN-1 AND TUMOR NECROSIS FACTOR PRODUCTION BY MONOCYTES AND/OR MACROPHAGES
[Antiinflammatory agents]

PATENT NO.: 5,317,019
ISSUED: May 31, 1994 (19940531)
INVENTOR(s): Bender, Paul E., Cherry Hill, NJ (New Jersey), US (United States of America)
Griswold, Don E., North Wales, PA (Pennsylvania), US (United States of America)
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Simon, Philip L., Randolph, NJ (New Jersey), US (United States of America)
Badger, Alison M., Bryn Mawr, PA (Pennsylvania), US (United States of America)
Esser, Klaus M., Downingtown, PA (Pennsylvania), US (United States of America)
ASSIGNEE(s): SmithKline Beecham Corp , (A U.S. Company or Corporation), Phildelphia, PA (Pennsylvania), US (United States of America) [Assignee Code(s): 23499]
APPL. NO.: 7-809,484
FILED: December 12, 1991 (19911212)
PCT: PCT-US90-03367 (WO 90US3367)
Section 371 Date: December 12, 1991 (19911212)
Section 102(e) Date: December 12, 1991 (19911212)
Filing Date: June 13, 1990 (19900613) ()

This application is a continuation-in-part of earlier U.S. application Ser. No. 07-365,349, filed Jun. 13, 1989, now abandoned.

FULL TEXT: 2713 lines

ABSTRACT

A method of inhibiting the production of interleukin-1 by monocytes and/or macrophages in a human in need thereof which comprises administering to such a human an effective, interleukin-1 production inhibiting amount of a diaryl-substituted imidazole fused to a second heterocyclic ring containing a nitrogen bridgehead atom wherein said second ring may also contain sulfur, oxygen or an additional nitrogen atom, and may contain

additional unsaturation.

This invention relates to a method of inhibiting the production of Tumor Necrosis Factor (TNF) by monocytes or macrophages in a human in need thereof which comprises administering to such mammal an effective, TNF production inhibiting amount of a compound of Formula (I) as described herein. The compounds of Formula (II) are generally described as diaryl-substituted imidazole fused to a second heterocyclic ring containing a nitrogen bridgehead wherein said ring may also contain sulfur, oxygen, or an additional nitrogen atom, and may contain additional unsaturation.

What is claimed is:

1. A method of inhibiting the production of interleukin-1 (IL-1) by monocytes and/or macrophages in a human in need thereof which comprises administering to such human an effective, IL-1 production inhibiting amount of a compound of the formula [See structure in original document] wherein: W sub 1 is --(CR sub 4 R sub 5)--(CR sub 6 R sub 7)--, --CR sub 5 double bond CR sub 7 --, --N double bond CR sub 7, --S(O) sub m -- or --O--;
n is 0 to 2;
one of R sub 1 and R sub 0 is 4-pyridyl or C sub 1-4 alkyl-4-pyridyl, provided that when R sub 1 is C sub 1-4 alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R sub 1 and R sub 0 is
(a) phenyl or monosubstituted phenyl wherein said substituent is C sub 1-3 alkylthio, C sub 1-3 alkylsulfinyl, C sub 2-5 1-alkenyl-1-thio, C sub 2-5 1-alkenyl-1-sulfinyl, C sub 3-5 2-alkenyl-1-thio, C sub 3-5 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio, C sub 1-4 alkyl or Z wherein Z is --S--S--Z sub 1 and Z sub 1 is phenyl or C sub 1-9 alkyl; or
(b) disubstituted phenyl wherein said substituents are, independently, C sub 1-3 alkylthio or C sub 1-4 alkyl; or
(c) disubstituted phenyl wherein one of said substituents is C sub 1-3 alkylsulfinyl, C sub 2-5 1-alkenyl-1-thio, C sub 2-5 1-alkenyl-1-sulfinyl, C sub 3-5 2-alkenyl-1-thio, C sub 3-5 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is C sub 1-2 alkoxy, halo, or C sub 1-4 alkyl;
(d) disubstituted phenyl wherein the substituents are the same and are C sub 1-3 alkylsulfinyl, C sub 2-5 1-alkenyl-1-thio, C sub 2-5 1-alkenyl-1-sulfinyl, C sub 3-5 2-alkenyl-1-thio, C sub 3-5 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio; or
(e) monosubstituted phenyl wherein the substituent is [See structure in original document] t is 0 or 1; W sub 1 and R sub 1 are as defined above; provided that:
(1.) when W sub 1 is --(CR sub 4 R sub 5)--(CR sub 6 R sub 7)-- then
n is 0 or 1; and
R sub 2, R sub 3, R sub 4, R sub 5, R sub 6, R sub 7, R sub 8, and R sub 9 are, independently, --H or C sub 1-2 alkyl; or
when n is 0, R sub 4 and R sub 5 together form an oxo; R sub 4 and R sub 5 may both be fluoro, or one of R sub 4 and R sub 5 is H and the other is OH; or
(2.) when W sub 1 is --CR sub 5 double bond CR sub 7 -- or --N double bond

CR sub 7 -- then
n is 1;
R sub 3, R sub 5, R sub 7 and R sub 9 are, independently, --H or C sub 1-2 alkyl; and
R sub 2 and R sub 8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring;
(3.) when W sub 1 is S(O) sub m then
m is 0, 1 or 2;
n is 1 or 2; and
R sub 3 and R sub 9 are, independently, --H or C sub 1-2 alkyl;
R sub 2 and R sub 8 are, independently, --H or C sub 1-2 alkyl or R sub 2 and R sub 8 together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring and
m is 0 and n is 1; and
(4) when W sub 1 is --O-- then
n is 1;
R sub 3 and R sub 9 are, independently, --H or C sub 1-2 alkyl; and
R sub 2 and R sub 8 together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring;

or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein:
W sub 1 is --(CR sub 4 R sub 5)--(CR sub 6 R sub 7)--, --CR sub 5 double bond CR sub 7 --, or --S(O) sub m --;
one of R sub 1 and R sub 0 is 4-pyridyl or C sub 1-2 alkyl-4-pyridyl, provided that when R sub 1 is C sub 1-2 alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R sub 1 and R sub 0 is
(a) monosubstituted phenyl wherein said substituent is C sub 1-2 alkylthio, C sub 1-3 alkylsulfinyl, 1-acyloxy-1-alkylthio; or
(b) disubstituted phenyl wherein said substituents are, independently, C sub 1-2 alkylthio, or
(c) disubstituted phenyl wherein one of said substituents is C sub 1-2 alkylsulfinyl or 1-acyloxy-1-alkylthio and the other is C sub 1-2 alkoxy, or
(d) disubstituted phenyl wherein the substituents are the same and are C sub 1-2 alkylsulfinyl or 1-acyloxy-1-alkylthio;

provided that:
(1.) when W sub 1 is --(CR sub 4 R sub 5)--(CR sub 6 R sub 7)-- then
n is 0 or 1; and
R sub 2, R sub 3, R sub 4, R sub 5, R sub 6, R sub 7, R sub 8, and R sub 9 are --H; or
when n is 0, R sub 4 and R sub 5 together form an oxo; R sub 4 and R sub 5 may both be fluoro, or one of R sub 4 and R sub 5 is H and the other is OH; or
(2) when W sub 1 is --CR sub 5 double bond CR sub 7 -- then
n is 1;
R sub 3, R sub 5, R sub 7 and R sub 9 are --H; and
R sub 2 and R sub 8 together represent a double bond in the B ring such

that the B ring is an aromatic pyridine ring;
(3.) when W sub 1 is S(O) sub m then
m is 0, 1 or 2;
n is 1 or 2; and
R sub 3 and R sub 9 are --H;
R sub 2 and R sub 8 are --H or R sub 2 and R sub 8 together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring and m is 0 and n is 1; and
(4) when W sub 1 is --O-- then
n is 1;
R sub 3 and R sub 9 are --H; and
R sub 2 and R sub 8 together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring;

or a pharmaceutically acceptable salt thereof.

3. The method of claim 2 wherein the compound is
2-(4-methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
2-(4-methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
2-(4-ethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
2-(4-ethylsulfinylphenyl)-3-(3-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
2-(4-methylthiophenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
2-(4-methylsulfinylphenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2a-]-imidazole;
2-(4-acetoxymethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
2-(trimethylacetylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
6-(4-methylthiophenyl)-5-(4-pyridyl)-2,3-dihydro-imidazo-[2,1-b]thiazole;
5-(4-methylthiophenyl)-6-(4-pyridyl)-2,3-dihydro-imidazo-[2,1-b]thiazole;
3-(4-methylthiophenyl)-2-(4-pyridyl)-6,7-dihydro-[5-H]-pyrrolo[1,2-a]imidzole;
2-(4-propylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-imidazole;
2-(4-methylthiophenyl)-3-(4-(2-ethyl)pyridyl)6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole;
2-(4-Mercaptophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-imidazole disulfide;

or a pharmaceutically acceptable salt of any one of the above compounds.

4. The method of claims 1 to 3 wherein the route of administration is parenteral, oral, topical, or by inhalation.

7/7/6 (Item 6 from file: 654)

Serial No.: 08/192,102
Art Unit: 1806

DIALOG(R)File 654:US PAT.FULL.
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02212789
Utility
METHOD OF DETECTING KAWASAKI DISEASE USING ANTI-TUMOR NECROSIS ANTIBODY

PATENT NO.: 5,075,236
ISSUED: December 24, 1991 (19911224)
INVENTOR(s): Yone, Kenji, Hino, JP (Japan)
Suzuki, Jun, Tokyo, JP (Japan)
Tsunekawa, Noriyuki, Hino, JP (Japan)
Kato, Arata, Sayama, JP (Japan)
Nakamura, Satoshi, Hino, JP (Japan)
Masegi, Tsukio, Hino, JP (Japan)
Kitai, Kazuo, Hino, JP (Japan)
Ichikawa, Yataro, Tokorozawa, JP (Japan)
ASSIGNEE(s): Teijin Limited, (A Non-U.S. Company or Corporation), Osaka, JP (Japan)
[Assignee Code(s): 83296]
APPL. NO.: 7-186,078
FILED: April 25, 1988 (19880425)
PRIORITY: 62-100010, JP (Japan), April 24, 1987 (19870424)
62-162233, JP (Japan), July 1, 1987 (19870701)
62-162234, JP (Japan), July 1, 1987 (19870701)
62-268218, JP (Japan), October 26, 1987 (19871026)
62-268219, JP (Japan), October 26, 1987 (19871026)
FULL TEXT: 971 lines

ABSTRACT

A method of confirming the diagnosis of Kawasaki disease in a patient which comprises assaying the patient's body fluid for the presence of elevated levels of a substance specifically bound by an anti-tumor necrosis factor monoclonal antibody.

What we claim is:

1. A method for confirming a diagnosis of Kawasaki disease in a patient comprising
contacting an anti-tumor necrosis factor antibody with a sample of body fluid from the patient.
detecting an amount of a substance which specifically binds the anti-tumor factor antibody, and
comparing the amount of the substance with that in a sample of body fluid taken from a normal, healthy person
wherein elevated levels of the substance are indicative of Kawasaki disease.

2. The method of claim 1 wherein the anti-tumor necrosis factor antibody

is an anti-human tumor necrosis factor monoclonal antibody.

3. The method of claim 2 wherein the anti-tumor necrosis factor monoclonal antibody is capable of
(a) neutralizing the cytotoxic effect of human tumor necrosis factor on L929 cells and the inhibitory effect of human tumor necrosis factor on fatty acid metabolism,
(b) recognizing epitopes contained in the 68th (Gly) to the 97th (Ile) amino acids in the amino acid sequence of human tumor necrosis factor, and
(c) specifically inhibiting binding of human tumor necrosis factor to a tumor necrosis factor receptor.

4. The method of claim 1 comprising
(a) contacting the body fluid sample with a first anti-tumor necrosis factor antibody immobilized on a solid support, then contacting the solid support with a labelled second anti-tumor necrosis factor antibody, or
(b) contacting the immobilized first anti-tumor necrosis factor antibody, the labelled second anti-tumor necrosis factor antibody and the body fluid sample simultaneously, and
detecting the amount of the substance which specifically binds anti-tumor necrosis factor antibody by detecting the amount of bound labelled antibody.

5. The method of claim 1 wherein the body fluid is serum or plasma taken from the patient.

7/7/7 (Item 7 from file: 654)
DIALOG(R)File 654:US PAT.FULL.
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02189643
Utility
TREATMENT OF INFLAMMATION
[Administering corticosteroid and at least one serine protease inhibitor, its salt or derivatives which bind with the mediators of mast or T-cells]

PATENT NO.: 5,215,965
ISSUED: June 01, 1993 (19930601)
INVENTOR(s): Lezdey, John, 976 Kingston Dr., Cherry Hill, NJ (New Jersey), US (United States of America), 08034
Wachter, Allan J., 9822 S. Grandview, Tempe, AZ (Arizona), US (United States of America), 85284 68000]
EXTRA INFO: Assignment transaction [Reassigned], recorded January 5, 1994 (19940105)

POST-ISSUANCE ASSIGNMENTS

ASSIGNEE(s): SONORAN DESERT CHEMICALS LIMITED LIABILITY COMPANY 6537 RUBY RED CIRCLE LAS VEGAS, NV 89108
Assignor(s): LEZDEY, JOHN -- signed: 12/28/1993; WACHTER,

Serial No.: 08/192,102
Art Unit: 1806

ALLAN -- signed: 12/28/1993
Recorded: January 5, 1994 (19940105)
Reel/Frame: 6823/0113
Brief: ASSIGNMENT OF ASSIGNORS INTEREST
Rep.: JOHN LEZDEY 701 HADDON AVENUE COLLINGSWOOD, NJ 08108

APPL. NO.: 7-755,300
FILED: September 05, 1991 (19910905)
DISCLAIMER: March 02, 2010 (20100302)

RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 591,752 filed Oct. 2, 1990, now U.S. Pat. No. 5,093,316 of Lezdey et al entitled "Treatment of Inflammation."

FULL TEXT: 263 lines

ABSTRACT

A method for the prophylaxis or direct treatment of mast cell implicated pulmonary diseases which comprises administering an effective amount of a corticosteroid and at least one serine protease inhibitor, its salts, derivatives or analogs which bind with the mediators of mast cells or T-cells.

We claim:

1. A method for the prophylaxis or direct treatment of mast cell implicated pulmonary disease in mammals which comprises administering by inhalation a composition of a synergistically effective amount of a corticosteroid and a natural or recombinant alpha 1-antitrypsin which inhibits the degranulation of mast cells and/or has an affinity to basophils, the mediators of mast cells or T-cells.

2. The method of claim 1 wherein said mast cell implicated pulmonary disease is asthma.

3. The method of claim 1 wherein said disease is bronchitis.

4. The method of claim 1 wherein said mediators comprise neutrophils, basophils and eosinophils.

5. The method of claim 1 wherein said mediators comprise cathepsin G and elastase.

6. The method of claim 1 wherein said corticosteriod is selected from the group consisting of triamcinolone acetonide, fluroandrenolide, prednisone, beclomethasone valerate, amcinolone, dexamethasone, betamethasone valerate, halocinonide, clocortolone and hydrocortisone valerate.

7. The method of claim 1 wherein said composition is non-aqueous.

8. A pharmaceutical composition for treatment of a patient suffering from a mast cell implicated pulmonary disease comprising the combination of an effective amount of a natural or recombinant alpha 1-antitrypsin which inhibits the degranulation of mast cells and/or has an affinity to basophils, the mediators of mast cells or T-cells, a synergistically effective amount of a corticosteroid, and a pharmaceutically acceptable carrier suitable for administration to the patient by inhalation therapy.

9. The composition of claim 8 wherein said corticosteroid is selected from the group consisting of triamcinolone acetonide, fluroandrenolide, prednisone, beclomethasone valerate, amcinolone, dexamethasone, betamethasone valerate, halocinonide, clocortolone and hydrocortisone valerate.

10. The composition of claim 8 which is non-aqueous.

7/7/8 (Item 1 from file: 148)
DIALOG(R)File 148:Trade & Industry Database(TM)
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06619729 SUPPLIER NUMBER: 14328047
Centocor's anti-TNF MAb for Crohn's disease. (monoclonal antibody against tumor necrosis factor alpha, CenTNF)
SCRIP World Pharmaceutical News, n1843, p21(1)
August 3, 1993

7/7/9 (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
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06871506 Genuine Article#: TC709 Number of References: 0
(NO REFS KEYED)
Title: NEW IBD MARKERS - DEFINITION OF DISEASE HETEROGENEITY
Author(s): TARGAN SR
Corporate Source: CEDARS SINAI MED CTR,CTR INFLAMMATORY BOWEL DIS,8700 BEVERLY BLVD,SUITE D4063,DAVIS BLDG/LOS ANGELES//CA/90048 (Reprint)
Journal: CANADIAN JOURNAL OF GASTROENTEROLOGY, 1995, V9, N6 (SEP-OCT), P 301-304
ISSN: 0835-7900
Current Contents Journal Announcement: CC CLIN, V23, N49
Language: ENGLISH Document Type: ARTICLE
Abstract: There is emerging evidence that serum and mucosal markers differentiate Crohn's disease from ulcerative colitis; moreover, subgroups can be defined within each disease. Subgroups have been defined on the basis of genetic, serum and mucosal markers, and are associated with different clinical phenotypes. Antineutrophil cytoplasmic antibodies (ANCA) define subgroups of patients with both

ulcerative colitis and Crohn's disease. A new serum marker, 20P-1, has been found in 60 to 70% of patients with Crohn's disease, 20% of ulcerative colitis patients and approximately 10% of the normal control population. The 20P-1 marker further stratifies the subgroups of patients defined by ANCA. In addition to serum markers, genes regulating production of the cytokine tumour necrosis factor (TNF)-alpha have been shown to be different across ulcerative colitis and Crohn's disease, and within the ulcerative colitis group. Serum markers may reflect differential mucosal inflammatory responses as is best shown by ANCA. B cell clones within the mucosa of 60 to 70% of patients with ulcerative colitis produce ANCA spontaneously. Studies currently underway demonstrate different TNF-alpha production within the mucosa of patients with Crohn's disease compared with ulcerative colitis patients. Correlation studies with TNF-alpha microsatellites (genes) are being performed. These markers are the focus of a trial using molecularly engineered products that are capable of inhibiting TNF-alpha to identify patients likely to respond to anti-TNF therapy. In this constantly evolving climate of understanding and treating inflammatory bowel disease, serum, mucosal and genetic markers as well as genetic associations are being formed to determine clinical phenotypes that may be differentially responsive to very selected treatment modalities. These advances highlight the likelihood that the various markers define different types of mucosal inflammation. The different types of mucosal inflammation will determine the response or resistance to certain types of therapeutic options.

7/7/10 (Item 2 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
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06108276 Genuine Article#: QC978 Number of References: 0
(NO REFS KEYED)
Title: ROLE OF CYTOKINES IN INFLAMMATORY BOWEL DISEASE
Author(s): HOANG P; FIASSE R; VANHEUVERZWYN R; SIBILLE C
Corporate Source: UNIV CATHOLIQUE LOUVAIN,SERV GASTROENTEROL,CLINST LUC,AV HIPPOCRATE 10/B-1200 BRUSSELS//BELGIUM/ (Reprint)
Journal: ACTA GASTRO-ENTEROLOGICA BELGICA, 1994, V57, N3-4 (MAY-AUG), P 219-223
ISSN: 0001-5644
Current Contents Journal Announcement: CC CLIN, V23, N09
Language: ENGLISH Document Type: ARTICLE
Abstract: The authors review the recent literature about the proinflammatory role of inteleukins-1,-2,-6,-8, tumour necrosis factor and interferon-gamma in Crohn's disease and ulcerative colitis, as well as their possible use to assess disease activity and to design new therapeutic approaches. Most cytokines were secreted in excess in inflammatory bowel disease. An imbalance between interleukin-1 and interleukin-1 antagonist might be a factor responsible of the chronicity of intestinal lesions. Circulating levels of interleukin-2 receptor are related to disease activity. Preliminary data on the

therapeutic use of antibodies to tumour necrosis factor are encouraging.

7/7/11 (Item 3 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
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06076932 Genuine Article#: QB258 Number of References: 0
(NO REFS KEYED)
Title: UPDATE OF IMMUNOMODULATORY THERAPY FOR INFLAMMATORY BOWEL DISEASE
Author(s): BERNSTEIN CN
Corporate Source: HLTH SCI CTR,GASTROENTEROL SECT,820 SHERBROOK ST,GB443/WINNIPEG/MB R3A 1R9/CANADA/ (Reprint)
Journal: CANADIAN JOURNAL OF GASTROENTEROLOGY, 1994, V8, N7 (DEC), P413-416
ISSN: 0835-7900
Current Contents Journal Announcement: CC CLIN, V23, N07
Language: ENGLISH Document Type: REVIEW
Abstract: For several decades corticosteroids were the only potent immunomodulatory agents effective and available for active inflammatory bowel disease (IBD). The past decade has seen an enhanced knowledge of the immune response in IBD and a better understanding of how common immunomodulatory agents work. Furthermore, more specific mediators of the abnormal immune response have been identified, so that therapy can be more targeted. Purine analogues have proven efficacy in achieving and maintaining remission in both Crohn's disease and ulcerative colitis. Methotrexate has proven efficacy in active Crohn's disease. Both of these classes of drugs requires weeks to mons of treatment before any benefit is seen. Intravenous cyclosporine is efficacious in acute severe ulcerative colitis and can settle active disease within days of administration. It is unclear whether oral cyclosporine offers any advantage at maintaining remission, once achieved. Oral cyclosporin in Crohn's disease has been proven to be ineffective at either achieving or maintaining remission; however, intravenous cyclosporine in Crohn's disease has not been rigorously tested. Newer immunomodulatory agents have been designed for specific targets, and in particular monoclonal antibodies that block the effects of interleukin-1, tumour necrosis factor-alpha and the T cell receptor are available for clinical trials. We are in an era of expanding therapeutic approaches to these diseases, including the refined use of readily available agents, the development of newer, more targeted agents and a broader understanding of how agents may be effectively used simultaneously or sequentially

7/7/12 (Item 4 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
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05804867 Genuine Article#: PJ308 Number of References: 32
Title: SERUM IMMUNOGLOBULIN G REACTIVE WITH ENDOTHELIAL CELLS IN

Serial No.: 08/192,102
Art Unit: 1806

INFLAMMATORY BOWEL DISEASE
Author(s): SAWYERR AM; POTTINGER BE; SAVAGE CO; BRADLEY NJ; HUDSON M; WAKEFIELD AJ; PEARSON JD; POUNDER RE
Corporate Source: WESTERN GEN HOSP,GASTROINTESTINAL LABS/EDINBURGH EH4 2XU/MIDLOTHIAN/SCOTLAND/ (Reprint); UNIV LONDON ROYAL FREE HOSP,DEPT MED/LONDON NW32QG//ENGLAND/; UNIV LONDON,SCH MED/LONDON//ENGLAND/; CLIN RES CTR,MRC,VASC BIOL SECT/HARROW/MIDDX/ENGLAND/
Journal: DIGESTIVE DISEASES AND SCIENCES, 1994, V39, N9 (SEP), P1909-1917
ISSN: 0163-2116
Current Contents Journal Announcement: CC CLIN, V22, N43; CC LIFE, V37, N43
Language: ENGLISH Document Type: ARTICLE
Abstract: Evidence of a humoral immune response to endothelium was sought in the sera of patients with inflammatory bowel disease. In an ELISA, IgG binding to human umbilical vein endothelial cells was found in 21% of Crohn's disease sera, 10% of ulcerative colitis sera, 6% of sera from patients with acute infective diarrhea, and 8% of normal control sera. The increased prevalence in Crohn's disease sera was significant ($P < 0.05$). IgG-endothelial cell binding was cell specific, was not Fc-mediated, and did not mediate complement-dependent cell lysis. It was not increased by pretreatment of cells with interleukin-1 or tumor necrosis factor. Endothelial cell binding was retained by IgG F(ab')(2) fragments from one of three reactive Crohn's sera, but none of three nonreactive sera. The low prevalence of this interaction, even in patients with immunohistochemically confirmed vasculitis, makes it unlikely that Crohn's disease is determined by a humoral autoimmune response to endothelium.

7/7/13 (Item 5 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
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04495089 Genuine Article#: KY380 Number of References: 34
Title: TUMOR NECROSIS FACTOR AND IL-1-BETA EXPRESSION IN PEDIATRIC PATIENTS WITH INFLAMMATORY BOWEL DISEASE
Author(s): OLSON AD; AYASS M; CHENSUE S
Corporate Source: UNIV MICHIGAN,MED CTR,DEPT PEDIAT,C6105 MIB,1500 E MED CTR DR/ANN ARBOR//MI/48109 (Reprint); UNIV MICHIGAN,MED CTR,DEPT PATHOL/ANN ARBOR//MI/48109
Journal: JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION, 1993, V16, N3 (APR), P241-246
ISSN: 0277-2116
Current Contents Journal Announcement: CC CLIN, V21, N20; CC LIFE, V36, N20
Language: ENGLISH Document Type: ARTICLE
Abstract: The local release of inflammatory mediators are intricately linked with initiation and propagation of the inflammatory reaction in ulcerative colitis (UC) and Crohn's disease. We have used immunohistochemical staining of colonic biopsies to determine the cell of origin and the location of the cells which synthesize of TNF-alpha and IL-1beta in patients with UC and Crohn's colitis. Patients were chosen from children aged 7-16 years, who had UC or Crohn's diagnosed

following review of colonic biopsies taken during colonoscopy. The patients reviewed had not received treatment for inflammatory bowel disease. Paraffin embedded colonic biopsies were sectioned, deparaffinized, and stained with mouse monoclonal IgG antibodies directed against human recombinant TNF-alpha and IL-1beta. The colonic lamina propria of all biopsies from patients with UC or Crohn's colitis was expanded with a mixed mononuclear, polymorphonuclear, lymphocytic, and plasmacytic infiltrate. Mononuclear cells distributed throughout the interstitium, stained prominently for both TNF-alpha and IL-1beta. Plasmacytes, polymorphonuclear leukocytes, small lymphocytes, and foamy macrophages did not stain for either TNF-alpha or IL-1beta. Transmigrating mononuclear cells in crypt epithelium also stained brightly for both TNF-alpha and IL-1beta. Colonic epithelial cells did not stain for either TNF-alpha or IL-1beta. We conclude that (a) expression of both TNF-alpha and IL-1beta is significantly increased in colonic biopsies from patients with both UC and Crohn's colitis, (b) mononuclear cells appeared to be the primary source for TNF-alpha and IL-1beta in patients with UC and Crohn's colitis, and (c) mononuclear cells synthesizing TNF-alpha or IL-1beta are distributed throughout both the intestinal crypts and interstitium.

7/7/14 (Item 6 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
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04444875 Genuine Article#: KV074 Number of References: 54
Title: CD4 ANTIBODY TREATMENT IN CROHNS DISEASE
Author(s): STRONKHORST A; TYTGAT GNJ; VANDEVENTER SJH
Corporate Source: UNIV AMSTERDAM,ACAD MED CTR,DEPT GASTROENTEROL,MEIBERGDREEF 9/1105 AZ AMSTERDAM//NETHERLANDS/ (Reprint)
Journal: SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY, 1992, V27, S194, P61-65
ISSN: 0036-5521
Current Contents Journal Announcement: CC CLIN, V21, N17; CC LINE- V36, N17
Language: ENGLISH Document Type: ARTICLE
Abstract: Immunologic changes may play a role in the pathogenesis of Crohn's disease. Whether these changes are the primary cause of the disease or secondary to the inflammatory response remains unknown. Activated T helper cells probably play a pivotal role in Crohn's disease, although no causative antigen has been identified. Possible targets for immunomodulating therapy should include neutralization of the antigens, deletion of reactive activated T cells or, less specifically, interference with the antigen-presenting process. New, humanized, monoclonal antibodies that interfere with the antigen-presenting process are now available for clinical investigation. In particular, CD4 antibody treatment seems of interest, in view of the predominant role of T cells in Crohn's disease. Finally, because tumor necrosis factor is necessary for granuloma formation, inhibition of this factor may be expected to improve disease activity in Crohn's disease.

Serial No.: 08/192,102
Art Unit: 1806

7/7/15 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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9752859 EMBASE No: 95295396
Ultrastructural immunogold localization of subcellular sites of TNF-alpha in colonic Crohn's disease
Beil W.J.; Weller P.F.; Peppercorn M.A.; Galli S.J.; Dvorak A.M.
Department of Pathology, Beth Israel Hospital, 330 Brookline Avenue, Boston, MA 02215 USA
Journal of Leukocyte Biology (USA) , 1995, 58/3 (284-298) CODEN: JLBIE ISSN: 0741-5400
LANGUAGES: English SUMMARY LANGUAGES: English
Tumor necrosis factor-alpha, a proinflammatory cytokine, might have an important role(s) in initiating, modifying, and/or sustaining chronic inflammatory processes such as those that characterize Crohn's disease, an inflammatory bowel disease of unknown etiology. We used an immunogold ultrastructural morphometric approach to localize tumor necrosis factor-alpha in colonic Crohn's disease biopsies. Tumor necrosis factor-alpha was present in seven cell types (fibroblasts, eosinophils, mast cells, macrophages, colonic epithelial absorptive cells, Paneth cells, neutrophils). Tumor necrosis factor-alpha-containing subcellular organelles included lipid bodies (fibroblasts, eosinophils, macrophages, mast cells, colonic epithelial cells, neutrophils), secretory granules (eosinophils, Paneth cells), phagolysosomes (macrophages, colonic epithelial cells), and Golgi structures and vesicle membranes (neutrophils). A gradient of extracellular tumor necrosis factor-alpha immunoreactivity surrounded eosinophils, mast cells, and macrophages. P values of gold counts/microm2 were significant for all cells, organelles, and extracellular spaces measured, and all positive structures significantly exceeded the background labeling density/microm2. Specificity controls (normal rabbit serum, tumor necrosis factor-alpha-absorbed primary antibody) either failed to label these sites or gave markedly reduced specific tumor necrosis factor-alpha labeling, respectively. These findings represent the first ultrastructural localization of the subcellular sites of TNF-alpha in vivo in seven cell lineages in human colonic tissues.

7/7/16 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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9699362 EMBASE No: 95249310
TNFalpha secreting cells in normal and diseases human intestine
Breese E.; MacDonald T.T.
Dept. of Paediatric Gastroenterology, St. Bartholomews Hospital, London EC1A 7BE United Kingdom
Advances in Experimental Medicine and Biology (USA) , 1995, 371/B (821-824) CODEN: AEMBA ISSN: 0065-2598
LANGUAGES: English

Serial No.: 08/192,102
Art Unit: 1806

7/7/17 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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9632603 EMBASE No: 95190436
Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2)
Van Dullemen H.M.; Van Deventer S.J.H.; Hommes D.W.; Bijl H.A.; Jansen J.; Tytgat G.N.J.; Woody J.
Department of Hepatogastroenterology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam Zuidoost Netherlands
Gastroenterology (USA) , 1995, 109/1 (129-135) CODEN: GASTA ISSN: 0016-5085
LANGUAGES: English SUMMARY LANGUAGES: English
Background and Aims: Increased concentrations of tumor necrosis factor (TNF), a potent proinflammatory cytokine, can be shown in the mucosa of patients with active Crohn's disease. Neutralization of TNF has been shown to decrease recruitment of inflammatory cells and granuloma formation in several animal models. The aim of this study was to investigate the safety and potential efficacy of an anti-TNF monoclonal antibody in the treatment of active Crohn's disease. Methods: Ten patients with active Crohn's disease that was unresponsive to therapy were administered a single infusion of an anti-TNF human/mouse chimeric monoclonal antibody (cA2) in an open-label treatment protocol while the baseline anti-inflammatory therapy was continued. Results: Eight patients showed normalization of Crohn's Disease Activity Index scores and healing of ulcerations as judged by colonoscopy within 4 weeks after treatment. One patient had a perforation after colonoscopy and recovered completely after surgery. One elderly patient showed a poor response. The average duration of response after a single infusion was 4 months. No adverse experiences related to cA2 were observed. Conclusions: The results support the hypothesis that TNF is of major importance in the pathogenesis of Crohn's disease. Treatment with cA2 was safe and may be useful in patients with Crohn's disease that is unresponsive to steroid treatment.

7/7/18 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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9627714 EMBASE No: 95179218
Significance of systemic endotoxaemia in inflammatory bowel disease
Gardiner K.R.; Halliday M.I.; Barclay G.R.; Milne L.; Brown D.; Stephens S.; Maxwell R.J.; Rowlands B.J.
Department of Surgery, The Queen's University of Belfast, Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ United Kingdom
Gut (United Kingdom) , 1995, 36/6 (897-901) CODEN: GUTTA ISSN: 0017-5749
LANGUAGES: English SUMMARY LANGUAGES: English
Quantitative and qualitative disturbances in faecal flora suggest a role for enteric bacteria and their products in the pathogenesis of inflammatory

bowel disease (IBD). This study investigated the hypothesis that systemically circulating endotoxins are of pathogenic significance in IBD by measuring antibody, cytokine, and acute phase protein responses. Systemic endotoxaemia was found in 88% patients with ulcerative colitis (n = 25) and 94% with Crohn's disease (n = 31) during clinical relapse. Systemic endotoxaemia correlated positively with anatomic extent and clinical activity of ulcerative colitis. Circulating tumour necrosis factor (TNF) was detected in 40% of patients with ulcerative colitis and 45% with Crohn's disease. Plasma TNF concentrations correlated with clinical and laboratory measures of disease activity and were associated with a surgical outcome to the disease episode. Plasma soluble TNF receptor p55 concentration correlated positively with disease activity and endotoxin core antibody concentrations. Plasma IgG endotoxin core antibody concentrations were significantly increased in patients with Crohn's disease and correlated with systemic endotoxaemia. The presence of systemic endotoxaemia, its correlation with disease activity, disease extent, and endotoxin core antibody concentration and the detection of circulating TNF and soluble TNF receptors all support a pathogenic role for endotoxins in IBD.

7/7/19 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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9619745 EMBASE No: 95172527
Tumour necrosis factor inhibition by oxpentifylline and intestinal inflammation in Crohn's disease (16)
Bauditz J.; Ruckert Y.; Raedler A.; Nikolaus S.; Lochs H.; Schreiber S.
Universitatsklinikum Charite, IV Medizinische Klinik Poliklinik, Department of Gastroenterology, 10117 Berlin Germany
Lancet (United Kingdom) , 1995, 345/8962 (1445) CODEN: LANCA ISSN: 0140-6736
LANGUAGES: English

7/7/20 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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9548423 EMBASE No: 95119956
Cytokine messenger RNA expression and proliferation status of intestinal mononuclear cells in noninflamed gut and Crohn's disease
Autschbach F.; Schumann G.; Qiao L.; Merz H.; Wallich R.; Meuer S.C.
Applied Immunology, German Cancer Research Center, Im Neuenheimer Feld 280, D-69120 Heidelberg Germany
Virchows Archiv (Germany) , 1995, 426/1 (51-60) CODEN: VARCE ISSN: 0945-6317
LANGUAGES: English SUMMARY LANGUAGES: English
T-cell activation and local cytokine production probably contribute to the pathogenesis of Crohn's disease. This study investigates the

proliferative status of intestinal mononuclear cells (MNC) and cytokine messenger RNA (mRNA) production in gut tissue sections from patients with Crohn's disease and noninflamed controls. mRNA in situ hybridization was performed using 33P-labelled riboprobes for human interleukin (IL)-1beta, IL-2, IL-4, IL-5, IL-6, tumour necrosis factor-alpha and interferon-gamma. The expression of the proliferation-associated antigen Ki-67 was analysed by immunohistochemical single and double staining. Compared with controls, where proliferation of MNC and cytokine expression was restricted to mucosal lymphoid follicles, inflamed gut tissue contained increased numbers of cells expressing cytokine mRNA, most prominently IL-1beta and IL-6, but also interferon-gamma and tumour necrosis factor-alpha. Proliferating T-cells were increased in number, and small amounts of IL-2-expressing cells were detected. IL-4 was expressed by a few cells exclusively in follicular germinal centres. IL-5 was negative. Proinflammatory cytokines are strongly expressed in situ in Crohn's disease and largely predominate over lymphokine mRNA. Our results provide in situ evidence of a local lymphocyte response in Crohn's disease with characteristics of a delayed-type hypersensitivity reaction.

7/7/21 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
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9477163 EMBASE No: 95049183
Novel drug therapies in inflammatory bowel disease
Debinski H.S.; Kamm M.A.
St Mark's Hospital, City Road, London EC1V 2PS United Kingdom
EUR. J. GASTROENTEROL. HEPATOL. (United Kingdom) , 1995, 7/2 (169-182)
CODEN: EJGHE ISSN: 0954-691X
LANGUAGES: English SUMMARY LANGUAGES: English
This paper reviews the published data on novel drug treatments for inflammatory bowel disease. Steroids that are topically active or rapidly metabolized have a definite therapeutic role and have fewer long-term side-effects than other steroids. Methotrexate can promote remission in approximately 50% of patients, but is less effective in maintaining remission. Cyclosporin is valuable for treating patients with severe ulcerative colitis but is less valuable for patients with Crohn's disease. None of the drugs that modify specific inflammatory mediators have proven efficacy but tumour necrosing factor and CD4 antibodies may be promising. In patients with distal colitis, lignocaine appears to be effective.

7/7/22 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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9367401 EMBASE No: 94305579
Inflammatory bowel disease in children
MacDonald T.T.
Dept. of Paediatric Gastroenterology, Medical College, St. Bartholomew's

Hospital, West Smithfield, London EC1A 7BE United Kingdom
CURR. OPIN. PEDIATR. (USA) , 1994, 6/5 (547-555) CODEN: COPEE ISSN: 1040-8703
LANGUAGES: English SUMMARY LANGUAGES: English

Inflammatory bowel disease in children and adults remains the most challenging problem in gastroenterology. There is an increasing body of immunologic and genetic evidence to suggest that Crohn's disease and ulcerative colitis are different diseases, but that once inflammation begins, many common secondary pathways of inflammation are initiated. The major recent conceptual advance is the observation that mice in whom different immunoregulatory pathways are disrupted develop an inflammatory bowel disease. In the case of interleukin-2 knockout mice, the lesion restricted to the colon, is virtually identical to ulcerative colitis in humans, and is initiated by the normal bacterial flora. Yet these mice possess anticolon antibodies, long-considered to be of pathologic significance in ulcerative colitis. These animal models will allow detailed longitudinal studies to be done, and less reliance will need to be placed on cross-sectional studies of chronically inflamed gut from patients.

7/7/23 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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9341467 EMBASE No: 94284445
Therapeutic applications of anti-TNF monoclonal antibodies
Bloxham D.P.
Celltech Ltd., 216 Bath Road, Slough, Berkshire SL1 4RN United Kingdom
EXPERT OPIN. INVEST. DRUGS (United Kingdom) , 1994, 3/9 (907-912)
CODEN: EOIDE ISSN: 1354-3784
LANGUAGES: English SUMMARY LANGUAGES: English

Tumour necrosis factor alpha (TNF) is a major product of activated macrophages which has a wide range of biological actions that have been implicated in a number of human diseases. This review presents the evidence that has been generated in animal models which suggests that TNF plays an important role in the pathology of septic shock, rheumatoid arthritis and inflammatory bowel diseases (Crohn's disease and ulcerative colitis). Anti-TNF antibodies either reduce or block the onset of symptoms in these models which suggests that this class of antibody may have useful therapeutic effects. Recent results of human clinical trials with a mouse antibody, BAYX 1351, and two recombinant antibodies, cA2 and CDP571, are discussed which indicate that the promising results in animals may be duplicated in man.

7/7/24 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE
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8896446 EMBASE No: 93200464
Tumour-necrosis-factor antibody treatment in Crohn's disease (3)

Derkx B.; Taminiau J.; Radema S.; Stronkhorst A.; Wortel C.; Tytgat G.; Van Deventer S.
Department Paediatric Gastroenterol., Academic Medical Centre, 1105 AZ Amsterdam Netherlands
LANCET (United Kingdom) , 1993, 342/8864 (173-174) CODEN: LANCA ISSN: 0140-6736 ADONIS ORDER NUMBER: 0140673693016112
LANGUAGES: English

7/7/25 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE
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8545481 EMBASE No: 92221361
Clinical advances in inflammatory bowel disease
Lichtenstein G.R.
Gastroenterology Division, Department of Internal Medicine, Hospital University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104-4283 USA
CURR. OPIN. GASTROENTEROL. (United Kingdom) , 1992, 8/4 (655-662) CODEN: COGAE ISSN: 0267-1379
LANGUAGES: English SUMMARY LANGUAGES: English

New clinical advances in inflammatory bowel disease are highlighted. Conditions that mimic the presentation of either ulcerative colitis or Crohn's disease are discussed along with the role that endoscopy, radiography, and histology play in establishing the correct diagnosis of each respective disorder. Assessment of Crohn's disease activity has progressed, with evaluation of soluble interleukin-2 receptor, serum tumor necrosis factor-alpha, fecal alpha1-antitrypsin clearance, erythrocyte sedimentation rate, IgG content of gut lavage fluid, and (III)In scintigraphy. Systemic complications associated with inflammatory bowel disease are reviewed, with particular attention to oral complication of Crohn's disease, complications resulting from a hypercoagulable state, bronchopulmonary manifestations, hematologic malignancies, and factors associated with intestinal perforation. Although the etiologic agents responsible for Crohn's disease and ulcerative colitis remain elusive we still continue to advance our knowledge base, making significant strides toward better understanding the pathophysiology of these two disorders, thus enabling us to better treat afflicted patients. These advances are established with hopes that we will soon unearth the cause and cure of both Crohn's disease and ulcerative colitis.

7/7/26 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE
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7212627 EMBASE No: 88212983
The role of IgG glycoforms in the pathogenesis of rheumatoid arthritis
Rademacher T.W.; Parekh R.B.; Dwek R.A.; Isenberg D.; Rook G.; Axford J.S.; Roitt I.

Serial No.: 08/192,102
Art Unit: 1806

Glycobiology Unit, Department of Biochemistry, University of Oxford, Oxford OX1 3QU United Kingdom
SPRINGER SEMIN. IMMUNOPATHOL. (Germany, Federal Republic of) , 1988, 10/2-3 (231-249) CODEN: SSIMD ISSN: 0344-4325
LANGUAGES: English
In conclusion, there is a shift in the population of IgG glycoforms towards those with a higher content of agalactosyl biantennary N-linked oligosaccharides in active rheumatoid arthritis (both juvenile and adult), tuberculosis, and Crohn's disease, but not in a variety of other rheumatological, inflammatory, or infectious conditions. This shift may contribute to disease pathogenesis both through immune-complex formation and through disturbance of a cellular network directed against the non-reducing terminal GlcNAc epitope. The precise pathology would in each case be modulated by the anatomical site(s) of production of such IgG, and also by the precise mechanism inducing this change in IgG glycosylation. Important amongst such mechanisms may be cross-reactivity between environmental and endogenous carbohydrate epitopes. It will be interesting to see if future research supports the idea that groups of diseases (e.g., rheumatoid arthritis, tuberculosis, Crohn's) are indeed related by a common aetiopathogenesis (i.e., G(O)).

7/7/27 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08613635 93323635
Tumour-necrosis-factor antibody treatment in Crohn's disease [letter]
Derkx B; Taminiau J; Radema S; Stronkhorst A; Wortel C; Tytgat G; van Deventer S
Lancet (ENGLAND) Jul 17 1993, 342 (8864) p173-4, ISSN 0140-6736
Journal Code: L0S
Languages: ENGLISH
Document type: LETTER

Set	Items	Description
S1	140	CROHN? AND ANTIBOD? AND TNF?
S2	89	RD S1 (unique items)
S3	115131	TNF? OR (NECROSIS(W)FACTOR? ?)
S4	1557365	ANTIBOD? OR IMMUNOGLOBUL? OR IG? ?
S5	13255	S4(10N)S3
S6	45	S5 AND CROHN? ?/DE
S7	27	RD S6 (unique items)

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Serial No.: 08/192,102
Art Unit: 1806

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          $10.50  6 Type(s) in Format  7
       $21.00  12 Types
        $0.00  View Fee
 $22.89  Estimated cost File440
        $0.48    0.008 Hrs File149
        $0.00  View Fee
  $0.48  Estimated cost File149
        $4.32    0.036 Hrs File434
        $0.00  View Fee
  $4.32  Estimated cost File434
        $2.58    0.043 Hrs File73
          $17.40  12 Type(s) in Format  3
          $17.40  12 Type(s) in Format  7
       $34.80  24 Types
        $0.00  View Fee
 $37.38  Estimated cost File73
        $1.56    0.052 Hrs File155
           $0.17  1 Type(s) in Format  3
           $0.17  1 Type(s) in Format  7
        $0.34  2 Types
        $0.00  View Fee
  $1.90  Estimated cost File155
        $0.30    0.002 Hrs File445
        $0.00  View Fee
  $0.30  Estimated cost File445
        OneSearch, 10 files,  0.216 Hrs FileOS
  $2.59  SPRNTNET
$117.57  Estimated cost this search
$119.71  Estimated total session cost   0.270 Hrs.
Logoff: level 39.10.16 B  11:43:29

DIALOG DISCONNECTED 00 40 00:00:16:05 1855 22

@ ae'fV4q~bmf+=E@V
NO CARRIER
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Serial No.: 08/192,102
Art Unit: 1806

d l8 1-3 cit, kwic;d his;log hold

1. 5,439,665, Aug. 8, 1995, Detection and treatment of infectious and inflammatory lesions; Hans J. Hansen, et al., 424/1.49, 153.1, 154.1, 172.1, 173.1; 530/391.3 [IMAGE AVAILABLE]

US PAT NO: 5,439,665 [IMAGE AVAILABLE] L8: 1 of 3

SUMMARY:

BSUM(42)

Included . . . treatment of, e.g., osteomyelitis; a composite of antibodies/fragments specific to B-cells and monocytes for the detection and treatment of, e.g., ▼ Crohn ▼ 's disease; a composite of ▼ antibodies ▼ /fragments specific to T-cells and B-cells for the detection and treatment of, e.g., sarcoidosis; a composite of antibodies/ fragments specific to. . .

2. 4,925,648, May 15, 1990, Detection and treatment of infectious and inflammatory lesions; Hans J. Hansen, et al., 424/1.53; 252/1; 424/9.34, 136.1, 153.1, 154.1, 178.1; 530/388.7, 388.73, 388.75, 389.6, 391.3, 402, 866 [IMAGE AVAILABLE]

US PAT NO: 4,925,648 [IMAGE AVAILABLE] L8: 2 of 3

SUMMARY:

BSUM(41)

Included . . . treatment of, e.g., osteomyelitis; a composite of antibodies/fragments specific to B-cells and monocytes for the detection and treatment of, e.g., ▼ Crohn ▼ 's disease; a composite of ▼ antibodies ▼ /fragments specific to T-cells and B-cells for the detection and treatment of, e.g., sarcoidosis; a composite of antibodies/fragments specific to monocytes. . .

3. 4,676,982, Jun. 30, 1987, Treatment of chronic inflammatory disease with polyvalent immunoglobulins; Alfred Hassig, 424/177.1, 130.1; 530/387.1, 390.5, 868 [IMAGE AVAILABLE]

US PAT NO: 4,676,982 [IMAGE AVAILABLE] L8: 3 of 3

SUMMARY:

BSUM(4)

It has now been found that chronic inflammatory diseases of this type, particularly ulcerative colitis and ▼ Crohn ▼ 's disease, may be successfully treated by intravenous administration of ▼ immunoglobulin ▼ . Accordingly, the present invention provides a method of treating chronic